Archives of Biochemistry and Biophysics 524 (2012) 43–47

Contents lists available at SciVerse ScienceDirect

Archives of Biochemistry and Biophysics

journal homepage: www.elsevier.com/locate/yabbi

Review

E-cadherin cell–cell communication in melanogenesis and during development of malignant melanoma

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ARTICLE INFO

Article history:
Available online 9 November 2011

Keywords:
Cadherins
Melanoma
Snail
AP1
Signaling
Cell–cell contact

ABSTRACT

Cell–cell communication is necessary for the crosstalk between cells that constitute multicellular organisms and is essential for cells to coordinate their physiological behavior to create cohesive tissues. Cellular crosstalk is not only controlled by molecules, like growth factors, hormones, ions and G-proteins, etc. but also by cell–cell contacts. These contacts are essential for intercellular communication and are involved in survival, apoptosis, proliferation, differentiation and homeostasis of entire tissues. In polarized epithelia of vertebrates, the adherent junction is part of the tripartite junctional complex that is localized at the juxtaluminal region, which includes tight junctions (including claudins, occludins, and zonula occludens proteins), desmosomal junctions (including desmogleins), and adherent junctions.

In focus of the manuscript are adherent molecules of the cadherin superfamily of the skin. In the normal epidermis, melanocytes and keratinocytes are mostly connected via E-cadherin, P-cadherin and H-cadherin [1–3]. Melanocytes that reside in the basal layer of the epidermis predominantly contain E-cadherin and H-cadherin, whereas those that reside in the hair follicles are rich in P-cadherin [2].

The regulation and role of E-cadherin during melanoma development will be the focus of this review.

Cell–cell communication in embryogenesis and melanogenesis

One important step in the development of the vertebrate embryo is neurulation (neurogenesis). The notochord induces its overlying ectoderm to develop into the neuroectoderm and subsequently the neural plate. The neural plate folds along its central axis to form a neural groove that is lined on each side by a neural fold (which is also called the neural plate border). The two neural folds fuse together and pinch off to become the neural tube. Some cells from the "apex" of the neural folds give rise to pluripotent neural crest cells that migrate throughout the embryo and give rise to a diverse set of cell types (Fig. 1). The development of specific cell types depends on two main migration pathways of neural crest cells. The cells migrating along the dorsoventral (DV)[1] axis between the neural tube and the somites differentiate into neurons and glial cells of the peripheral nervous system. These cells form the spinal ganglia, the ganglia of the autonomic nervous system and other diverse neurons [4,5]. The cells migrating along the dorsolateral (DL) axis between the somites and the ectoderm do not move as rapidly and simultaneously with the cells that move along the DV axis, and they give rise to melanoblasts that later differentiate into melanocytes. In the DL axis, melanoblasts first migrate through the forming dermis. They cross the basement membrane of the skin, settle down in the epidermis in contact with the basement membrane and differentiate into melanocytes [6]. Additionally, the skeletal and muscular components in the head, bones, tendons, connective tissues, endocrine tissues and adipose tissues arise via neural crest cells of the DL axis. Non-classical melanocytes are located in many diverse sites, including the eye, inner ear, meninges, bones, and heart [7–11], and use migration routes that differ from classical melanocytes [12]. Remarkably, neural crest-derived cells can give rise to numerous cancers of great clinical significance.

We will review the development of neural crest-derived melanocytes because they are the precursors of melanoma. The development of melanocytes has been studied in detail in mice. The distinct developmental steps leading to the appearance of fully differentiated melanocytes occur between mouse embryonic days E9 and E17. First, neural crest cells migrate from the neural tube to arrive at the dorsolateral surface by E9–E9.5. The melanoblast markers are not upregulated until E10.5–E11 in the DL migratory axis [13]. The mouse melanoblasts begin populating the dermis and epidermis and producing pigment at E16.5 [14]. Induction of the

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[1] *Abbreviations used:* DV, dorsoventral; DL, dorsolateral; NCSC, neural crest stem cells; BMPs, bone morphogenic proteins; FGF, fibroblastic growth factor; EMT, epithelial-to-mesenchymal transformations; bHLH, basic helix-loop-helix; RGM, radial growth phase melanomas; VGM, vertical growth phase melanomas; SSM, superficial spreading melanomas; NMM, nodular melanomas; MET, mesenchymal–epithelial transition; sh, short hairpin; MMPs, matrix metalloproteinases; NRAGE, neutrophin receptor-interacting melanoma antigen.

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doi:10.1016/j.abb.2011.10.020

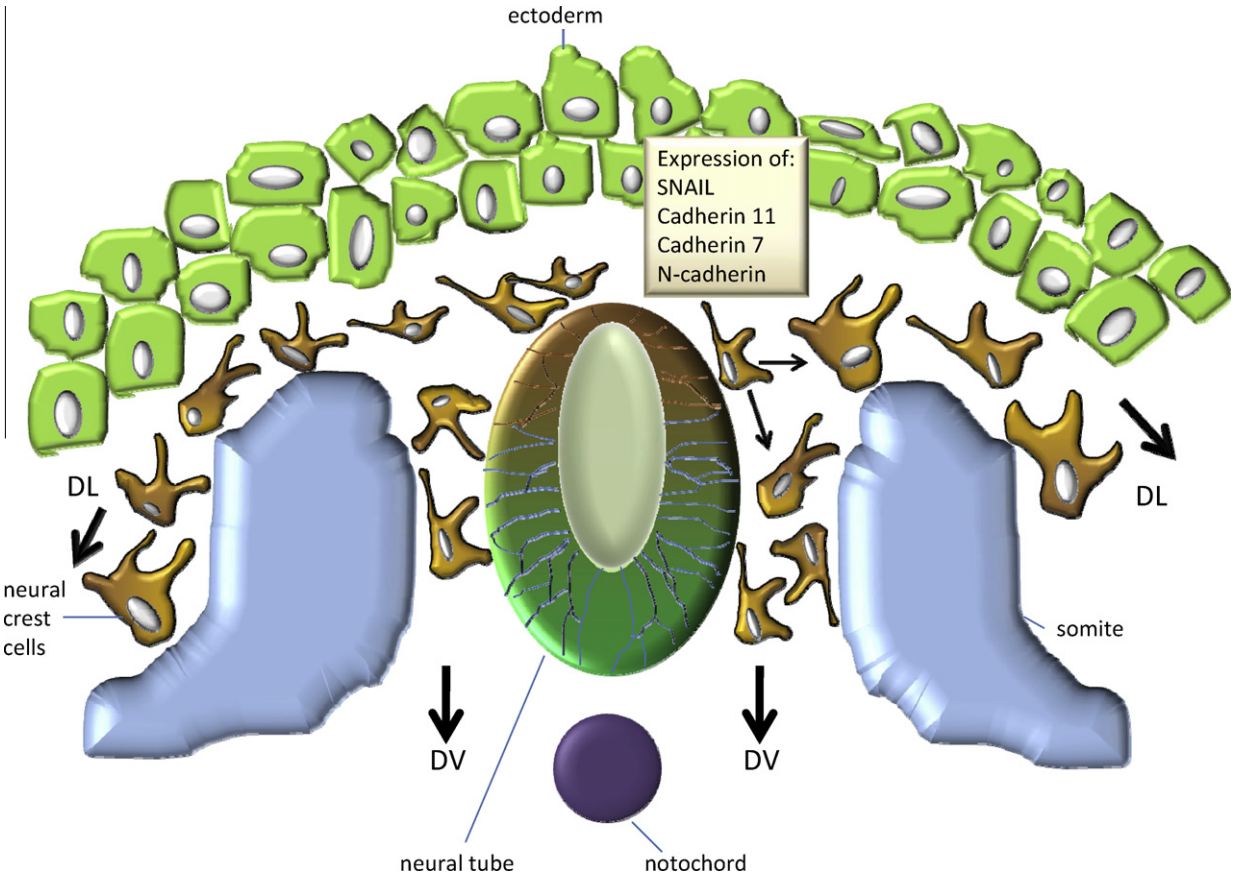

Fig. 1. Schematic overview of the migration pathway of neural crest cells. The cells of the embryonic neural crest (brown), which are derived from the upper region of the initial epithelial neural tube (brown-green), delaminate from this epithelium, acquire motility and invasiveness after losing E-cadherin and cadherin 6B expression, and disperse throughout the embryo and eventually throughout the body of the resulting organism. Precursor cells of melanocytes migrate along the dorso-lateral (DL) axis. The cells that differentiate into neurons and glial cells of the peripheral nervous system migrate along the dorsoventral (DV) axis (modified from [53]).

neural crest involves a complex set of extracellular signals that transform the fate of cells lying along the medio-lateral and anterior–posterior axes of the embryo. The molecules and signaling pathways that mediate this first step of differentiation of neural crest stem cells (NCSC) include the WNT/β-catenin pathway, BMPs (bone morphogenic proteins) and their antagonists, the FGF (fibroblastic growth factor) family, molecules of the NOTCH pathway and the transcription factors SNAIL, SLUG, TWIST, PAX3 and SOX10. These molecules are usually conserved throughout mammalian evolution [15]. The molecule SNAIL is a main regulator of E-cadherin expression in embryogenesis and during melanoma.

The SNAIL gene family and E-cadherin during embryogenesis

SNAIL belongs to a family of "zinc finger" transcription factors and was originally identified in *Drosophila melanogaster*. Our understanding of how E-cadherin production is regulated has been improved by the identification of its transcriptional repressors. *SNAIL* gene family members are widely used as the earliest indicators of neural crest formation because they mark cells undergoing epithelial-to-mesenchymal transformations (EMT). The normal and pathological versions of this process involve changes in cell shape, enhanced motility and fundamental alterations in the gene expression profiles of cells undergoing EMT. *SNAIL* genes function as transcriptional repressors that regulate gene expression during EMT. SNAIL binds to the E-cadherin promoter and directly represses E-cadherin expression, thereby promoting neural crest cell migration [16]. The downregulation of cell adhesion molecules, such as E-cadherin, promotes the delamination, or the exit, of neural crest cells from the neural plate and is concomitant with the commencement of their migration throughout the body. Neural crest cells that undergo EMT downregulate other adhesion molecules such as NCAM, cadherin 6B and N-cadherin and upregulate cadherin 7, and cadherin 11 [17–20]. This "cadherin switch" demonstrates that a regulated balance of cadherin expression is needed for migration. The cells in our bodies retain genetic pathways required for developmental processes, and cancer can arise if embryonic signaling pathways are reactivated later in life. Altered adhesive profiles also apply to the genesis of tumors such as melanoma. Among all proteins, the transmembrane E-cadherin molecule plays a preeminent role organizing epithelial versus mesenchymal phenotypes.

Cell–cell communication during melanoma development

The role of E- and N-cadherin during melanoma

In healthy human skin, the crosstalk between melanocytes and keratinocytes is important in the epidermis. The normal phenotype and controlled proliferation of melanocytes is strictly regulated by keratinocytes via E-cadherin. The extracellular domains of separate E-cadherin molecules are tethered together, and the intracellular domain is anchored to the actin fibers of the cytoskeleton via a complex of catenins. Therefore, by knitting together the actin cytoskeletal networks of adjacent cells, E-cadherin molecules help a tissue cell sheet resist mechanical forces that might otherwise tear